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EXPERIMENTAL "RESTRAINT ULCER" IN THE WHITE RAT. III. STUDY AND ANALYSIS OF THE PART PLAYED BY CERTAIN PSYCHOLOGICAL FACTORS

S. Bonfils, G. Liefooghe, X. Gelle, M. Dubrasquet, A. Lambling, with the technical collaboration of N. Enjolvy

Translation of ""ULCERE' EXPERIMENTAL DE CONTRAINTE DU RAT BLANC III. MISE EN EVIDENCE ET ANALYSE DU ROLE DE CERTAINS FACTEURS PSYCHOLOGIQUES", Revue Francaise d'Etudes Cliniques et Biologiques, Vol. 5, 1960, pp 571-581

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16. Abstract: Rats studied during restraint were found to go through three motor phases: continuous, uncontrolled agitation; paroxymal, intermittent agitation; and prolonged inertia. There was no correlation between the release reaction and the incidence of ulcers, mortality, or weight loss. It may be concluded that the release reaction is not the pathogenic stimulus in restraint and is not related to it. A quantitive assessment of the psychological stimulus imposed by enforced immobilization was attempted on 503 normal and 400 vagotomized rats, confined in five different volumes from 360 to 7350 ml. The smaller the restraint space, the more frequent the ulcers. There was a statistically significant difference between normal and vagotomized rats, the slope of the regression line being flatter in the latter.

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EXPERIMENTAL "RESTRAINT ULCER" IN THE WHITE RAT

III. STUDY AND ANALYSIS OF THE PART PLAYED BY CERTAIN PSYCHOLOGICAL FACTORS

S. Bonfils, G. Liefooghe, X. Gelle, M. Dubrasquet, A. Lambling with the technical collaboration of N. Enjolvy

[Gastroenterology Center, Bichat Hospital (A. Lambling Dept.), Gastroenterology Research Unit of the National Institute of Hygiene, Paris]

The close relationships between gastric motility, secretion, /571* and trophicity on the one hand and cerebral activity on the other have been studied for more than fifty years; the results observed supported both the Pavlovian and psychoanalytic theories of peptic ulcer disease in man.

However, in the accounts of the innumerable methods likely to trigger gastric lesions in animals, it is rare to find a study of the psychological factors involved or even an analysis of the animal's behavior during experiments. Only tests specifically oriented in this direction, such as those of Levrat and Lambert [12] for example, escape this criticism.

This is partly due to underrating the importance of psychological processes in the animal. It is also because of the difficult techniques used in such studies: some are rapidly lethal, some involve complex and multiple stimuli, of which many employ pathogenic (toxic, surgical or other) actions whose casual relationship with the gastric lesion is evident and appears to be predominant.

From this viewpoint the "restraint ulcer" technique is of quite remarkable facility: the triggering stimulus is very easy to bring about and reproduce over long series; the lethality it

*Numbers in the margin indicate pagination in the foreign text.

causes is very low; variations in frequency of lesions as a function of the duration of restraint enable both protective and aggravating factors to be studied [4, 7, 10, 13]; pathogenic agression uses neither surgery nor drug or toxic action.

These being the circumstances, it was easy for us first to analyze the animal's behavior. The results of this study, supplementing our previous reports [2, 5, 11] led us to minimize the importance of general motor reactions as a pathogenic factor. The "restraint" stimulus acts by itself; this was confirmed by our observations upon increasing the volume of restricted space, and repeating the stimulus on the same animal.

Thus our various conclusions invoking the importance of the psychological factor in the genesis of the experimental "restraint ulcer" seem to have a solidly foundation.

I. ANALYSIS OF THE RAT'S BEHAVIOR DURING RESTRAINT: THE RELEASE REACTION

a) Overall Description

Generally speaking, we observe in the majority of animals a succession of three stages:

1. Continuous uncontrolled agitation: this phase coincides first of all with the animal's awakening from anesthesia which, even without stress, is accompanied by violent motor reactions. But this agitation continues far beyond waking, for a period of between fifteen and forty-five minutes. We see violent starts throughout the body, alterating with sharp head and paw movements. The corset confines these movements, as does the absence of something for the paws to push against.

2. Intermittent paroxysmal agitation. This stage comes next. It is characterized by movements of the haunches, paws, /572 and head, of fairly short duration (five to twenty seconds). Between attacks the animal is completely at rest, its eyes closed, with increasing inertia as restraint continues.

However if one merely strokes its muzzle lightly or squeezes a paw the animal has a clear waking reaction or even a paroxysmal agitation crisis.

The presence in the laboratory of rats undergoing other experiments, squeaking and struggling during injections or when they are sacrificed, seems to increase the frequency of attacks. This frequency falls off as restraint continues.

When the restraint is kept up for seven hours, the animal retains this behavior as long as the experiment lasts. If, however, it is continued to twenty-four hours, the third stage occurs in 50% of cases, but the time it begins varies widely from one animal to another.

3. Prolonged inertia: the rat makes no movement at all. It makes a slight withdrawal movement when a paw is squeezed, and usually tries to bite when its muzzle is touched.

However, this is not total exhaustion: once released, the animal usually recovers normal motility in a short time: three to four hours. A small number of rats (less than 10%) at this stage die within the twenty-four hours following removal of the restraint in spite of being released.

4. Lethality during restraint. Mortality is remarkably low, which is adequately explained by the benignness of the pathogenic factor imposed on the animal: the absence of a prior fast, and parenteral hydration at the beginning of restraint. It is 5.3% for the twenty-four-hour restraint and 3% for the seven-hour restraint.

On this point we may note that certain rats seem literally unable to bear restraint: they very rapidly enter the prolonged inertia phase and die in fairly short periods, almost always having substantial gastric lesions. This explains the fact that mortality is not substantially greater for the twenty-four-hour than for the seven-hour restraint.

b) Quantitative Assessment of Release Reaction

The stereotype of the animals' agitation, even during Phase I, makes it easy to set up apparatus to record the number of paroxysmal attacks to establish a parallel, if any, between the size of the motor reaction and the frequency of ulceration.

Technique

Figure 1 shows the apparatus used. Pneumographic recording is done under positive (not negative) pressure due to the heavy drag on the animal's rear paws. The paws must be stretched by the conducting wire as, during attacks, the rat tends to draw its paws underneath it.

[Figure indistinct in original.]

Figure 1: Motor activity of the rat during restraint: recording techniques.

The frequency of accidents during recording attests to the intensity of the paroxysms. Actually, for a given stage, the intensity is fairly constant (Figure 2). This is particularly valid for Phase II, dominant in this quantitative system of assessment of the release reaction.

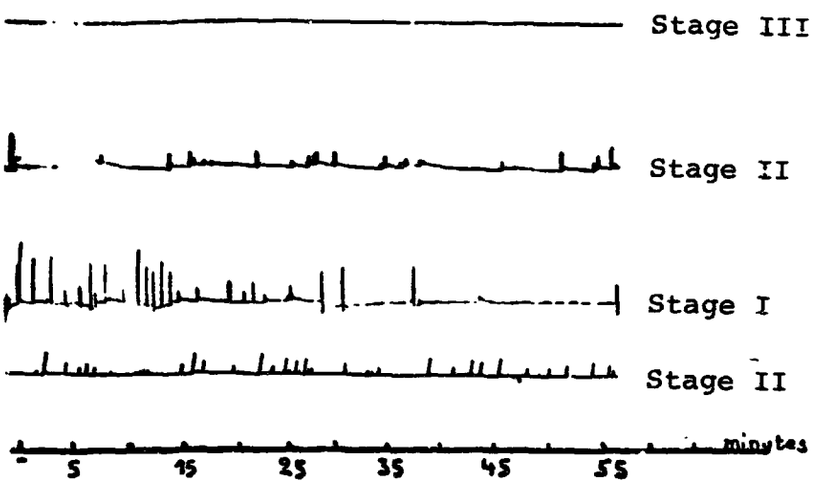

Figure 2. Motor activity of rat during restraint: traces of three phases.

We thus confined ourselves to counting the number of paroxysmal attacks without regard to their intensity which, provided it exceeded a certain threshhold value, was arbitrarily fixed once and for all. /573

Results

One hundred and ten recordings were made, namely: seven-hour restraint: 42, with recording throughout restraint; twenty-four hour restraint: 68, recording for the first four and last three hours.

a) Intensity of release reaction in the first four hours.

For the first four hours of all the control series (seven hours and twenty-four hours) we obtain the following results:

80% of the animals had 106 to 260 motor attacks, and 50% of them had 125 to 225 motor attacks.

In the first four hours of all series (seven hours and twenty-four hours) which underwent additional treatment or surgery (adrenalectomy, mephrectomy, corticotherapy) we observe a distribution strictly identical to that of the controls.

Of the total of sixty-five animals belonging to the two above groups, we obtain a bell-shaped distribution curve showing the stability of the release reaction through the series that showed wide variations in frequency of gastric lesions.

b) Intensity of release reaction during seven-hour restraint (Figure 3).

The motor attacks could be evaluated throughout the duration of restraint in forty-two animals, either controls or those who had undergone the above treatments.

The bell-shaped distribution is absolutely regular: 71% of the rats had 90 to 330 motor attacks.

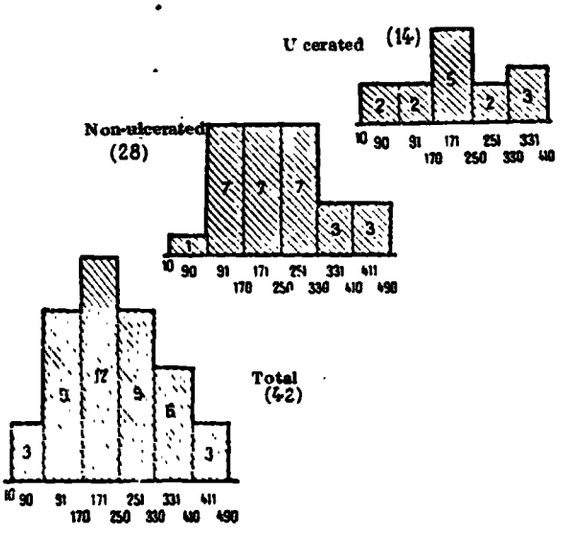

Figure 3. Motor activity of the rat during restraint: frequency of paroxysmal attacks over seven hours, all series combined.

Although we distinguish between animals with ulceration (14) and animals without ulcertation (28) the type of distribution remains identical: the preceding percentage is respectively 65% and 75%.

Interpretation /574

Although the results are from a fairly small number of animals, they permit us to conclude that the frequency of restraint ulcers bears no relationship to the intensity of the release reaction. A

basic argument in support of this opinion will be supplied by the data obtained when we varied the volume of restraint, which we will discuss further on.

The same applies to mortality during restraint: decrease occurs in subjects with earlier-than-average inertia whose motor reaction is sometimes confined to the agitation on waking from anesthesia.

II. VARIATIONS IN FREQUENCY OF GASTRIC ULCERATION ACCORDING TO THE VOLUME OF RESTRAINT SPACE: THE RESTRICTION IMPOSED

Although motor reaction to immobilization is not the causative factor of restraint ulcer, we are compelled to recognize that immobilization, by itself, is a pathogenic element. We should remember that the rat is an animal with spontaneous and considerable motor activity: its daily travel amounts to several kilometers. When we restrict this travel we are certainly introducing a grave perturbation to the lifestyle of the animal.

This "imposed restriction" is obviously maximal during the restraint obtained by a corset, as we described above. However, when we introduce the animal into cages of different volumes with varying degrees of free space, it is possible to give this "imposed restriction" a variable quantitative value.

We might then think that, if the incidence of gastric ulcers is a function of this restriction, modifications in frequency of lesions will be observed according to the different volumes of restraint. This is the basis of the tests described above, supplementing our previous tests [2].

Technique

After anesthesia and injection of physiological serum, in the same manner as for the standard restraint, the rat is introduced into one of the chosen spaces, kept there fasting for twenty-four hours, then sacrificed.

The study was a comparative one of five hundred and forty-three normal she-rats and one hundred and one vagotomized she-rats (weight of animals between 140 and 190 g). The vagotomy was performed abdominally etween ten and fifteen days before the start of the experiment.

Five types of restraint volume were studied: 360, 560, 750, 1260, and 7350 ml. We should remember that the volume of a 170 gram rat is 180 ml.

These spaces were delimited inside ordinary cages by moving mobile partitions placed along the cage's width, and glass rods threaded through the holes in the chicken-wire to delimit the available height and length (Figures 4, 5, and 6). However, the 7350 ml volume is the whole of one small cage in which the animal is completely free.

Schematically, the volume characteristics are as follows:

1260 ml: width 7 cm; length 23 cm; height 7.8 cm; the rat can turn around easily.

7650 ml: width: 5 cm; length, 21 cm; height, 7.3 cm; the rat turns around with some difficulty, however he can play with the glass rods which make a horizontal ceiling and slide them to free himself if they are not joined together by a strip of sticking-plaster.

560 ml: width 7 cm; length and height determined by the rat itself whose shape is molded by the succession of glass rods.

360 ml: width, 4.5 cm; length and height according to the same factors as the 560 case.

The paroxysmal release reactions do not take place for volumes 1260 and 760. They are slight or non-existent for the other three spaces; in any event very much smaller than for the standard restraint.

[Figure indistinct in original.]

Figure 4. Restrictive cage; side view of volumes 360 ml and 560 ml.

The results, condensed in Table I, were analyzed according to the period when the experiment was performed. This was essential since tests were spread over two years.

Three periods are distinguished: period I, all of 1958; period II, first semester 1959; period III, second semester 1959.

[Figure indistinct in original.]

/575

Results

A number of facts may be deduced by examination of Table I. A statistical analysis was made, to be published in a subsequent article. Here we will give only the main conclusions and the mathematical substantiation.

Figure 5. Restrictive cage: top view of 360 ml volume.

[Figure indistinct in original]

Figure 6. Restrictive cage: side view of volumes 750 ml and 1260 ml.

We would first note that, in this table, the standard restraint is defined as reducing the cage to the volume of the rat, i.e. 180 ml.

1. Intact Animals (543 she-rats)

a) For the first six volumes chosen, ulceration frequency observed had no statistically significant variations as a function of the periods in question ($p < 0.05$). The stimulus triggered by a precise "imposed restriction" is thus remarkably stable. b) There is a regular increase of ulcerative frequency according to reduction in cage volume. The relationship between the two phenomena is statistically significant ($p < 0.001$). c) It is easy to see, from Figure 7, that, provided the reciprocal of the volume of the cage (1/V) is plotted on the abscissa, the six points are in almost perfect alignment (including point $1/180 \times 10^5$ of the standard restraint).

The "ulcer frequency/imposed restriction" relationship is expressed by a regression line whose equation (in probits) is

the following: $y = 3.81 + 0.0041\ x$. The interval of confidence is fairly narrow, about 4-5% according to the points on the line.

2. Vagotomized Animals (141 she-rats)

a) The increase in frequency of ulceration as a function of reduction of restraint space is a statistically established phenomenon ($p < 0.01$). b) In the graphic plotting of the phenomenon, the points are equally aligned, but according to a regression line with a different slope than that of the normal rats: $y = 4.09 + 0.0022\ x$.

The interval of confidence is slightly larger than with normal rats.

TABLE

Restraint Volume (ml)	Period	Normal (543)			Vagotomized (141)		
		No.	No. with ulcers	Percent with ulcers	No.	No. with ulcers	Percent with ulcers
180 (standard restriction)	I	137	118	86.1	27	17	63
	II	18	17	91	17	10	58.8
	III	24	20	83.3	—	—	—
	Total	179	155	86.5	44	27	61.4
360	I	51	24	47			
	II	17	8	47	26	10	38.5
	III	30	13	43.3			
	Total	98	45	45.9			
560	I	29	9	31			
	II	6	2	33.3	26	9	34.6
	III	17	5	29.4			
	Total	52	16	30.7			
760	I	31	6	19.3			
	II	17	7	41	13	3	23
	III	19	6	31.5			
	Total	67	19	28.3			
1 260	I	51	7	13.7			
	II	24	8	33.3	32	7	21.9
	III	21	4	19			
	Total	96	19	19.7			
7 350	I	51	6	11.7	—	—	—

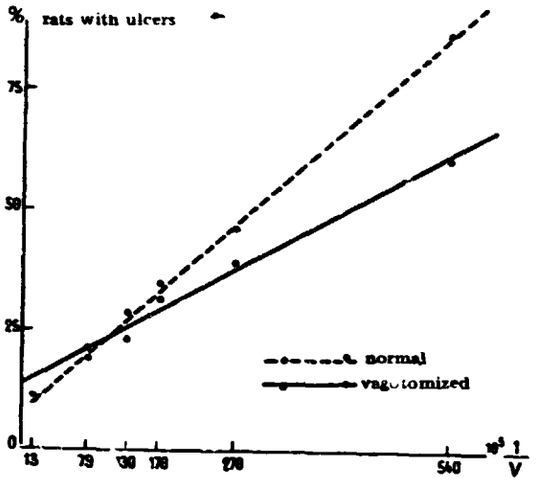

FIG. 7.

Figure 7. Relationship between frequency of ulceration and volumetric restriction in normal and vagotimized rats.

Interpretation

The existence of a mathematical relationship between the /576
reduction in the volume of restrictive space and the frequency of ulceration (with both the intact and the vagotomized animals) enables us to conclude that: 1) the release reaction plays no effective role in the survival of ulcers since it is absent for two of the volumes chosen, while the results obtained in these cases agree with the other points on the regression line; 2) in the standard restraint, the stimulus is confined strictly to the restriction imposed, since, for the case of a restricting volume identical with the rat's volume, the results harmonize with those of the five other spaces studied; 3) the restraint causes a stimulus measurable according to the space allowed for the animal.

What pathogenic mechanisms are triggered by the imposed restriction? One first finding stands out: the facts observed make a sharp distinction between the restraint ulcer and the gastric lesions observed during Selye's general adaptation syndrome: the almost-quantitative reaction to the "restraint"

stimulus is quite different from the threshold provoked by stress as Selye conceived it. We will come back to this point later.

The involvement of the vagus nerve is evident. Comparison between vagotomized and intact rats can be made as follows: 1) the ulcerating frequency in the 482 normal animals (excluding the 7350 ml volume which has no counterpart in the vagotomized animals) is statistically different from that of the 141 vagotomized animals ($p = 0.005$); 2) this difference is in fact significant only for the standard restraint ($V = 180$ ml) ($p < 0.001$) but the predominance of the animals in this series has a repercussion on the overall analysis of the results; 3) however, the two regression lines, whose origins are almost the same, have clearly different slopes. In other words, the more intense the /577
restraint stimulus the more effective the vagotomy. This seems to imply that, for low-intensity stimulus, the pathogenic reaction does not pass through the vagus. As this stimulus increases, the vagus is more and more involved, and largely responsible for the quantitative nature of the gastric lesion response. It thus acts as the transmitter of a nerve influx which cannot be of central origin.

Note that, in a recent publication, Brodie et al. [6] although observing a reduction in ulcerative frequency after vagotomy during a twenty-four-hour restraint, believe that their results are not significant. Apart from the fact that their series have less than fifteen animals, it may be assumed that these authors were working under conditions where the stimulus was not sufficiently large for the vagus effect to be dominant and hence vagotomy effective.

We will not analyze here the pathogenic factors involved in the vagotomized animal (thus also in the intact animal apart from the vagal factor). We will also leave for a later article the study of how the vagus effects the gastric wall.

III. EFFECT OF REPEATED RESTRAINT PERIODS: REDUCTION OF REACTIVITY TO STIMULUS

The high frequency of lesions with twenty-four-hour restraints leads one to assume that both the stimulus and the organic response are constant.

The phenomenon seems connected in particular to the species of animal since Brodie [6] in the United States recently found exactly our lesion percentage (86%) in the rat, while this figure is 92% in the mouse, 46% in the guinea pig, and only 4% in the hamster.

Confining our investigations to the rat, we were however, able to observe that restraint did not always give rise to strictly identical reactions. There is, in fact, at least one circumstance where the method's reproducibility is wanting, as the results show a clear drop in lesion incidence: when the restraint is repeated [2].

When we renew the restraint periods with the same series of animals, taking care to avoid as far as possible any nutritional impact of the fasting periods, we observe a clear reduction in the percentage of animals with ulcers.

Certain elements lead us to think that "psychological deconditioning" rather than physiological adaptation is involved.

Technique

1. Repeated Restraint (139 she-rats).

After the initial restraint period of twenty-four hours, the animal, instead of being sacrificed, is set free for forty-eight hours in a communal cage with normal feed. After this time it undergoes a second restraint. It can then either be sacrificed or released temporarily for another forty-eight hours until the next test.

We experimented on three batches of animals containing about fifty rats each, undergoing, respectively, two, three, and four periods of constraint before being sacrificed (series R2, R3, and R4).

A quantitative evaluation of the release reaction was performed according to the technique described for some of these animals.

Examination of the stomach after sacrifice raises difficult problems. It was stated in a prior article [5] that a full ulcer cure, after a twenty-four-hour cessation of restraint, was certain only past the ninth day after release. Now, the sacrifice after the second restraint period was on the fourth day, still taking the end of the first restraint as the point of departure. In theory, thus, there is interference between the lesions produced by the successive restraints.

Indeed, we indicated that it is possible to distinguish the stage of lesion macroscopically (recent acute ulcer, cicatrizing ulcer, etc.); moreover, on the fourth day, depending on the first restraint, a maximum of only 10% acute lesions persists. We can thus say that the majority of the acute ulcers observed in series R2 depend on this second restraint. This reasoning seemed all the more valid for <u>all</u> the series of repeated restraints as sources of error act to increase the frequency of lesion. As our results show (we shall see) a decrease of this frequency, disappearance of any error could only make our results still more significant.

To conclude this technical preamble, we will thus state that we centered our analysis on the frequency of recent acute ulcers.

2. <u>Controls</u> (10 she-rats).

To evaluate any influence of the nutritional factor, we subjected the animals to twenty-four hours of total fast separated by forty-eight-hour phases of normal feeding. The rats were

isolated by group. Three such periods were traversed. Instead of a fourth period, a true restraint was made, after which the animals were sacrificed. /578

TABLE II

Series	No. of Animals	Recent Ulcers		Cicatrizing Ulcers		Normal Stomachs	
		Percentage	Snedecor	Percentage	Snedecor	Percentage	Snedecor
24-hour one rest unit	179	86.5	79-91	0		13.5	9-21
Repeated restraint							
R2	46	73 9	54-80	10.9	3-22	15.2	6-27
R3	45	51.1	34-63	37.8	23-50	11,1	5-24
R4	48	25	13-38	43.7	28-57	31.3	18-44
Controls (rhythmic fast then one restraint)	10	70	35-93	0	—	30	7-65

Results

1. Ulcerative Frequency /578

The results are shown in Table II. It appears that the frequency of acute ulcers diminishes as restraint is repeated. The phenomenon is statistically significant ($p = 0.001$).

The increase in the percentage of cicatrizing ulcers seems also to depend on reiteration, but in a much more probative manner. This is evidently a result of the relatively small number of acute ulcers in series R3. The frequency of unaffected stomachs clearly increases in series R4.

Moreover it is evident that rhythmic fast gives no protection from restraint ulcer.

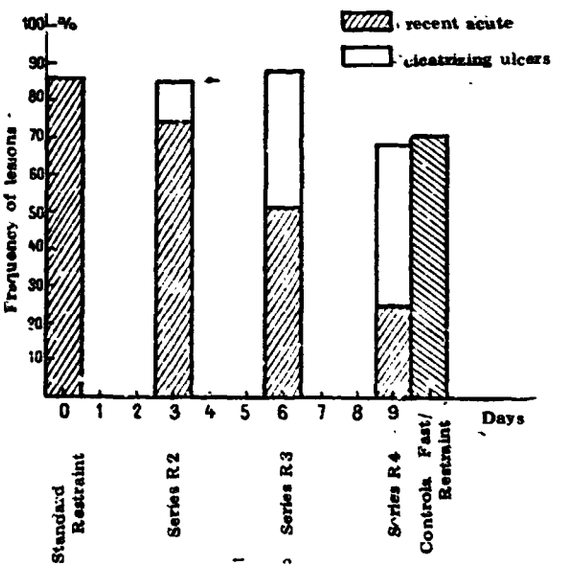

Figure 8. Repeated restraint and frequency of gastric lesion

2. Nutritional Effects

We will simply give, by way of indication, the weight loss (as a percentage of initial weight) in various series, calculated from the groups of ten to thirty animals. Remember that our rats, of the female sex, originally weighed between 140 and 190 g.

Standard restraint: 9.4%

Restraint to various volumes:

360 ml: 13%
560 ml: 10%
760 ml: 10.7%
1260 ml: 9%
7350 ml: 10.2%

Repeated restraint

R2: 14.5%
R3: 17.8%
R4: 19.2%

Controls (rhythmic fast after last restraint): 17.9%

3. Release Reaction

The agitation was recorded only for the first four hours.

Series	No.	80% of rats between n and n attack	50% of rats between n and n attack
Standard restraint	40	106 - 260	125 - 225
Series R2	17	100 - 350	150 - 325
Series R3	20	70 - 400	125 - 375
Series R4	18	75 - 260	125 - 275

Thus, at least for the first four hours of restraint, repeating does not lead to motor incurement. On the contrary, it seems that the number of animals with an intense release reaction is particularly high in series R2 and R3.

Interpretation

The repeated restraint was undertaken in the beginning to induce chronic gastric ulcerations, and the restraint periods could appear as the equivalent of ulcer growth. /579

The results were the reverse of what we expected and focused our interest in quite another direction.

The reduction in the frequency of acute ulcers when restraint is repeated is evident. This was despite substantial malnutrition which appears responsible for the high mortality observed in series R3 and R4.

What is the reason for this decline in frequency? The first hypothesis would be that the intermittent fast engendered by the repeated restraints could act either by diminishing organic reactivity by malnutrition, or by causing endocrinous or other adaptation.

The results of the control series contradict both these assumptions: by comparison with series R4, the drop in weight is almost identical (17.9% as against 19.2%) while the ulcerating frequency is clearly (and statistically) different (70% against 25%).

Another hypothesis, towards which we conducted our previous tests, involves a psychological phenomenon. At first sight, the slightest sensitivity (or reactivity) to the "restraint" stimulus should be manifested by a reduction in agitation, which is not the case.

But we have already shown that release reaction and ulcer frequency are quite independent of one another; that certain rats, in particular, die very quickly in a state of inertia, and were affected with substantial gastric lesions.

Conversely, it seems that certain animals are completely immune to the restriction imposed. An argument in this direction is supplied by the percentage of normal stomachs in various series. Thus, on the third day after releasing a 24-hour restraint, we find 20% normal stomachs. This percentage represents stomachs unaffected by restraint (14%) and inconsequential lesions which would be rapidly cured. The imposition of a second restraint in this third day (series R2) only brings down this percentage to 15.2%, i.e. to the percentage of unaffected stomachs at the initial restraint. This result is only possible if the stomach injured at the second restraint were primarily in animals who had suffered the first restraint. Conversely, it does seem that the majority of rats who did not react to the first stimulus did not react to the second either; they are thus spontaneously refractory subjects.

For series R3 and R4 the analysis is more complex since the phenomena overlapped, but also argues in this direction.

At any event, we can bring no definitive argument to bear in favor of "psychological deconditioning" caused by repeated restraint. We will simply say that, given the importance of the "imposed restriction" stimulus in the genesis of restraint ulcer, this deconditioning is altogether plausible.

Finally, we will point out that Brodie, practicing daily (18 out of 24 hours) repeated restraint, observed a frank aggravation of lesions and appearence of ulcers on the rumen. This technique (like that of psychogenic ulcer tests on the rat by Levrat and Lambert [12]) involves substantial malnutrition since the fall in weight is 22% on the second day and 30% on the fourth. At this stage the drop in organic resistence seems to us to play an evident facilitating role.

IV. GENERAL CONCLUSION

Psychological factors in the restraint ulcer were demonstrated in various ways, and the arguments brought to bear are of unequal value.

A. The animal's general reactions have no correlation with the frequency of ulceration. This is true in particular for the rhythm of the agitation periods marking the release reaction. This is also true for the weight loss observed during restraint, and for the mortality.

We cannot say, as we did not study the point, whether this is also true for adrenal hypertrophy and thymus reduction which, according to Selye [14] occur in experimental tests of this kind. We will note, however, that the absence of protective power of the hypophysectomy vis-a-vis gastric ulcers [6], and the quantitative nature of the gastric lesion response acccrding to the volume of restricted space, do not argue in favor of involvement of the general adaptation syndrome in restrain ulcer genesis.

B. The mathematically-established correlation between volume of restriction and ulcerative frequency seems to us, in fact, the leading argument in favor of a psychological process - physical aggression is totally suppressed.

The psychogenic action is probably not exclusive, as the results on vagotomized animals show. The non-vagal element could be endocrinous; but it could also simply be another mode of response to the psychological stimulus. Only later tests will tell us. /580

It seems that we have the following causal series: imposed restriction - psychogenic involvement - vagal hyperactivity connected quantitatively to the extent of restriction.

This vagal hyperactivity unquestionably affects secretion as we have already shown [2-11]. Is this its only gastric effect? We do not know. In any event we will recall that these facts are very similar to certain observations by Dragstedt [9]: if, in a normal man, nocturnal secretion of twelve hours is 18.6 mEq, it is 30 mEq in the imprisoned normal man and 63 mEq during a duodenal ulcer.

Similarly, it is certain that, in man, a number of psychological situations, coinciding with an ulcer, are - literally or symbolically - lived through like a restraint [8].

Thus it does indeed seem that according to its psychogenic element through vagal transmission, the restraint ulcer is more similar to the human situation than any other experimental ulcer technique.

C. Finally, the drop in ulcerative frequency according to repeated restraint only takes on its true interest in the light of the preceding facts.

From the psychological viewpoint, we are confronted with true "deconditioning". This however is more or less a function of individual or racial factors, which are increasingly being related to lethality.

REFERENCES

1. Bonfils S., Rossi G., Liefooghe G., and Lambling A. Gastric "restraint ulcers" in the white rat. Journée d Et. Dlin. et Biol., Paris, 1958 (Rev. Franc. Études Clin. et Biol., 1958. 3. 709).

2. Bonfils S., Liefooghe G., Rossi G., and Lambling A. The experimental "restraint ulcer" in the white rat. Analysis of main determinant factors. Arch. App. Digest., 1959, 48, 449.

3. Bonfils S., Liefooghe G., Rossi G., and Lambling A. Restraint ulcer in the white rat. Modifications of lesion incidence by various surgical and pharmacodynamic procedures. C.R. Soc., 1957, 151, 1149.

4. Bonfils S., Rossi G., Liefooghe G., and Lambling A. Experimental "restraint ulcer". I: Methods, lesion incidence, modifications by certain technical and pharmacodynamic procedures. Rev. Franc. Études Clin. et Biol., 1959, 4, 146.

5. Bonfils S., Richir C., Potet F., Liefcoghe G., and Lambling A. Experimental "restraint ulcers" in the white rat. II: Antomopathology of gastric lesions and various visceral lesions. Development of ulceration after releasing the restraint. Rev. Franc. Études. Clin. et Biol., 1959, 4, 888.

6. Brodie D.A. and Hanson H.M. A study of the factors involved in the production of gastric ulcers by the restraint technique. Gastroenterology, 1960, 38, 353.

7. Debray C., Le Querler Y., and Mouvier M. Effect of fresh Vichy water on "restraint ulcers" in the rat. La Presse Thermale et Climatique, 1959, 96,167.

8. M'Uzan M.de and Bonfils S. Psychosomatic clinical forms of peptic ulcer. Rev. Franc. Études Clin. et Biol.,1960, forthcoming.

9. Dragstedt L.R. Etiology of peptic and duodenal ulcer. Lyon Chirurgical, 1955, 2, 129.

10. Fontan M., Houcke E., and Deregniaux P. Effects of derived amines of phenothiazine on the "restraint ulcer" in the white rat. Lille médical, 1959, 4, 647.

11. Lambling A. , Bonfils S. The ulcer in a restraint situation. Aertzliche Forsch., 1960, 14, 208.

12. Levrat M and Lambert R. Experimental ulcers obtained by modifying the environment in the rat. Arch. Mal. App. Digest., 1959,48,591.

13. Rossi G., Bonfils S., Liefooghe G., and Lambling A. A new experimental ulcer technique in the white rat: restraint ulcer. C.R. Soc. Biol., 1956, 150, 2124.

14. Selye H. The general adaptation syndrome and the diseases of adaptation. J. Clin. Endocr., 1946, 6, 117.